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Original article

An evaluation of the strengths and weaknesses of a register of newly diagnosed rheumatoid arthritis, 1986–2010

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Abstract

Objectives. To evaluate the strengths and weaknesses of a register of management and outcomes of recently diagnosed RA, and allow comparisons between rheumatology centres on good clinical practice and guidelines.

Methods. A register of newly diagnosed RA was initiated in 1986 in nine different regions of England, later expanded to UK-wide membership in 2002. Standardized data collection includes disease activity, function, radiological damage, therapy, hospitalizations, major comorbidity and mortality. A centralized database generates individual reports and comparative data for each centre yearly. Aims have been compared with actual achievements and any changes over 25 years.

Results. Thirty rheumatology centres have recruited 2866 patients. Study outputs have included peer-reviewed scientific publications and contributions to the recent National Audit Office report on RA. Referral times into secondary care have changed little over 25 years, but time to initiation of drug therapies has decreased. Delays between publication of clinical trial evidence and management guidelines and their implementation in normal clinical practice are illustrated by relatively infrequent use of combination therapies at diagnosis. Consecutive case recruitment, centre participation and follow-up were reportedly compromised by local funding issues. Centre participants report a benefit from feedback of actual clinical practice compared with recommended standards of care.

Conclusions. Most of the original objectives have been achieved. Cohort studies based predominantly in District General Hospitals provide unique insights into the natural history and impact of RA, its management, the translation of research findings into clinical practice and provide participating centres with important clinical governance and professional development opportunities.

Key words: Rheumatoid arthritis, RA outcomes, Disease registry, DMARDs.

CLINICAL SCIENCE

Introduction

RA registers and long-term inception cohorts have been established since the 1960s in several countries, mainly in northern Europe (Sweden, Norway, The Netherlands and UK), and more recently in southern Europe and the USA. The ACR recommended in 1999 [1] the collection of a minimum data set in order to monitor the progression of disease and response to treatment. The British Society of Rheumatology (BSR) indicated that prescription of novel biological agents for RA should be conditional on the collection of a similar data set to determine eligibility for treatment and monitoring of adverse events. The BSR Biologics Register has since provided invaluable data on

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toxicity of these drugs, but by definition in highly selective and more severe disease [2].

The proposal for a registry of newly diagnosed RA in the UK arose from the recognition by a group of rheumatologists that, first, the optimal management for RA is still a major challenge and improvements are unlikely to come from randomized controlled trials (RCTs) alone, which can only address a limited number of key issues. Second, it was clear that there was wide variation in clinical practice in the measurement of clinical outcomes and health status of RA and in therapies offered. Several important improvements in the care of RA have emerged since the late 1970s and early 1980s. A number of new and more effective DMARDs have been introduced, and since 2000, highly effective but expensive biological agents for RA have become available. Large joint replacement surgery has now become a common and routine procedure in more severe disease. International and national guidelines on the management of RA have been published by several professional bodies, patient support groups have become well organized and proactive, and equitable access to appropriate care has become a greater issue in rheumatology. What is less certain is how clinical practice has responded to these changes.

The introduction of Clinical Governance within the National Health Service (NHS) has created a need for the collation of data on activity and outcomes at the national as well as the local level. Such data are required to facilitate the planning and provision of health care for RA patients and to inform the development of appropriate and realistic standards against which future activity can be audited.

National Service Frameworks (NSFs) are now a mandatory part of the management of certain other chronic diseases (e.g. diabetes), but such a framework is at present not available for rheumatological conditions, apart from a section on the management of osteoporosis in the NSF for elderly care.

The Scottish Intercollegiate Guideline Network (SIGN) [3], BSR [4], Arthritis and Musculoskeletal Alliance (ARMA) [5] and National Institute of Clinical Excellence (NICE) [6] have published the best clinical management guidance and standards of care of early RA and recommended a minimum data set for clinical audit and effectiveness purposes. Many professional bodies representing national and international rheumatology have accepted that registers can improve current knowledge about RA and inform specialists about key aspects of treatment.

The main aim of this report is to describe the strengths and weaknesses of a registry of early RA initially set up in the 1980s, and how this has changed over 25 years. The initial and any subsequent objectives are compared with actual achievements.

Methods

Background

With the above factors in mind, nine rheumatologists with experience in observational studies and from separate regions in England agreed in 1986 to register all newly diagnosed RA patients before starting DMARD therapy and follow these patients yearly using a basic and simple standardized assessment form. This initiative was based on the only two other cohort studies in the UK started in the 1960s, both single-centre studies with ultimately limited outcome analysis because of small numbers at follow-up [7, 8].

The primary aim of the Early RA Study (ERAS) was to establish a database of long-term clinical data in order to monitor management and outcomes of patients with RA in the UK. It was envisaged that this resource would enable comparisons between centres and contribute to the development of good clinical practice and guidelines and clinical governance issues.

Secondary aims were research issues and included examination and generation of prognostic factors for RA outcomes. The Oxford Centre for Evidence-Based Medicine recognizes inception cohorts with long-term follow-up as the optimal research design for prognostic studies and not RCTs. Cohort studies provide the information needed to evaluate differences between treatment strategies for RA in the long-term, reflecting true-to-life clinical practice and the development of prognostic markers. Such cohorts also allow for assessments of the effect of comorbidities on outcome, increasingly recognized as important since RA is known to be an independent risk factor for cardiovascular disease. With increasing awareness of the role of psychological and social factors in RA progression, there is a need to explore the processes by which such factors affect drug concordance or compliance, disease progression and quality of life. Outcomes include disease activity and severity using a variety of standard measures, medication usage and adverse events, structural joint damage (radiological scores and need for orthopaedic surgery), work disability, mortality and prevalence of concurrent pathology and resource use. It is the only RA inception cohort from different regions in England reflecting clinical practice of the 1980–90s before the biologic era with 5- to 15-year outcomes [9–11].

The group achieved its initial targets of recruiting at least 1000 patients, with follow-up data in $>$90%, by 1994. Some centres opted to stop recruiting new patients at this time and concentrate resources on follow-up, partly due to local changes in personnel and circumstances, while other centres continued to recruit new patients.

Based on the success of this group, a critical mass of rheumatologists proposed an expansion of the network into a wider membership, the Early RA Network (ERAN), which started in 2002. The primary and secondary aims were similar and the data collection template retained the most useful and appropriate features of ERAS, discarding redundant variables. ERAN has retained an open policy, encouraging participation of new centres, resulting in the representation of clinical practice across the UK in the 21st century to explore changing practice and outcomes with the developing therapeutic agents in both the short and long term. ERAN allows rapid feedback of clinical practice and short-term outcomes through the provision of annual

reports to participants, so that any actual changes in the clinical management can be monitored over time.

Results combine many separate but inter-related issues of importance to rheumatologists, patients and health planners. In addition, this cohort allowed the facilitation of design and execution of nested studies by providing statistical information required for study design and permitting the identification of potential research subjects. The network is now supported by 30 rheumatology centres in England, Wales, Scotland and Eire, and has recruited 1151 patients (2002 to end 2009).
The criteria for patient registration:

- early RA (<3 years);
- earlier use of DMARDs; and
- patient consent.

A minimum data set includes:

- demographics and diagnostic/classification citeria of RA [12];
- 28-joint disease activity score (DAS-28) [13] and severity using standard measurements (X-ray damage);
- standard patient-administered health questionnaires [HAQ and Short Form-36 (SF-36)];
- concomitant disease and extra-articular manifestations;
- concomitant RA medications—reasons for change, duration and toxicities;
- paid work status; and
- hospitalizations and all other interventions.

Rheumatologists or nurse practitioners complete case report forms. Data are collected at baseline, 3–6 months, 12 months and then annually. The data are monitored by a data co-ordinator using source data verification, working towards the standards set out in the International Conference on Harmonisation Good Clinical Practice [14], to ensure that the highest possible standards are maintained and to ensure the credibility of the data.

The infrastructure is well developed using a novel data management system developed by the Medical Research Council Clinical Trials Unit (London, UK) and Hertfordshire University. Although the ERAS and ERAN software systems were developed separately, input variables are compatible for combined data analysis, with the addition of disease activity and quality of life variables for ERAN (DAS-28 instead of the original DAS, physician global assessment and SF-36). The group is managed through steering, audit, education and research commmittees, and meets at least annually at an annual general meeting and education training days.

Results

Comparisons have been made between initial and subsequent aims and objectives agreed to by the clinicians involved and actual achievements. Various dimensions have been assessed and include recruitment numbers, missing data, reporting, audit of guidelines, access to national and Department of Health databases, patient involvement and collaborations (Table 1).

The group achieved its initial patient recruitment targets with good follow-up and reasons for withdrawal were largely ascertained. Some centres have opted to stop recruiting new patients once a critical mass was achieved for that centre and to concentrate resources on follow-up. Recruitment of new rheumatology centres has slowed in recent years, not because of lack of interest or inertia, but mainly because of local funding issues.

An important issue for disease registers is the quality of follow-up. The reasons for withdrawal were expected and mainly unavoidable. However, the numbers lost to follow-up, despite attempts to trace patients, were slightly higher than the initial target.

A major contribution to the quality of follow-up data of this database is the link with other national databases. The National Health Service Central Register holds computerized records of all patients registered with general practitioners in England and Wales. The date and main cause of death are based on death certificates, which allow the recording of three other contributing causes and three comorbid conditions. These are coded by the Office for National Statistics (ONS) [15] and provided electronically to the network within 1 month of death, using the International Classification of Disease, 10th Revision (ICD-10). Only patients who have moved from the UK permanently fail to be recorded under this system.

An important finding on mortality in RA was that not only was cardiovascular disease the most common cause of death, and increased compared with population figures, but also was the most common cause in the first 7 years of RA [16]. An unexpected finding was the number of deaths from RA-associated interstitial lung disease (RA-ILD) in 6%. This was the only classical extra-articular manifestation of RA recorded on death certificates as the main or contributing cause of death. A subsequent report on the natural (treated) history of RA-ILD in this cohort found an annualized incidence of 4.1/1000 (95% CI 3.0, 5.4), a 15-year cumulative incidence of 62.9/1000 (95% CI 43.0, 91.7) and the median survival following diagnosis of RA-ILD was only 3 years [17]. Comparing the incidence of vasculitis in RA suggested a reduction from the 1980s to 2000s [18].

Management guidelines

In the past 10 years, the profession has witnessed the publication of a number of guidelines and standards of care. This group has contributed data in the generation of some of these and is in the process of continual assessment of these against actual practice. The database contributed towards a major section of the National Audit Office (NAO) report on patients with RA, mainly on treatment times and orthopaedic interventions [19]. An important finding was that the rate-limiting step to start of therapy was in fact the patient's self-referral to primary care, not delays to secondary care, and starting DMARDs in secondary care was timely [20].

In an evidence- and cost-based review of rational use of new and existing DMARDs, Kremer's guidance was centred on the initial use of MTX, which could be followed

Table 1 Initial aims and subsequent achievements

Dimension	Aims	Achievements
Recruitment	1986–1992: at least 1000 patients, 2002–2010: >2000	1986–1994: 1460 1995–2001: 255 2002–2009: 1151 Total = 2866
	Consecutive patients with RA	Difficult to verify
Follow-up	Lost to fup <5% (Fup)	Deceased (32%), unable 14% (reason known, e.g. moved, comorbidity, own choice, etc), lost to Fup = 7%, 53% attending
Database	Continuity of management team	Same core staff of three since 1992
	Recording of main clinical and lab variables:	Missing data (despite reminders)
	HAQ, joint score, DAS, ESR 100%	= 94%
	Start/stop dates for drug therapies 100%	= 89%
	Regular yearly feedback to each centre	Standardized reports have been generated yearly for each centre. Feedback indicated that the most useful were:
	Individual centre data:	
	Recruitment and Fup	Comparisons of each centre with total
	Clinical data	Variations in clinical data within each centre by recruitment year
	Missing data	
	Comparative data—demographics, employment, benefits and deprivation index	Variations consistent with local demography
Clinical practice Use of DMARDs Guidelines	Data on initial type and timing of DMARD and steroid use Yearly feedback to centres and yearly analysis of adherence to guidance	Database has contribution to: NICE [6] appraisal of biologic therapies BSR [4] guidelines NAO [18] report on RA
Outcome measures: Orthopaedic surgery	HES [22] data: date and type of all orthopaedic interventions, with primary and secondary diagnostic codes—100%	1986–95: data on orthopaedic interventions obtained from patients and patient records since national HES diagnostic codes were incomplete 1995–2009: combined database and HES data from each centre—in progress
Mortality	Date and ICD-10 codes for cause of death (ONS [15])—100%	99%
Reporting	One to two peer-reviewed publications per year	1992–2010: 30 peer-reviewed publications
	At least one abstract at each of the yearly BSR, EULAR and ACR meetings	Achieved (>100 abstracts)
Patient and public involvement	Regular patient involvement in network design and management	NRAS [24] members on committees ARMA [5] membership
Collaborations	Share data with appropriate and professional organizations for the ultimate benefit of patient care	2002—NICE appraisal-biologic therapies [27] 2004—BSR guidelines 2009—NAO Report on early RA

Fup: follow-up.

by SSZ alone or with HCQ, then LEF or biologics [21]. The consensus of European rheumatologists was similar and recommended both the use of at least two DMARDs (one being MTX) and persistent disease activity, based on the DAS-28, before biologics should be considered [22]. The latter has been strongly supported by the BSR in recently published guidelines on the management of early RA [4]. Clinical trial data, however, suggest that patients do better with early combination therapy, especially triple therapy, with or without steroids. It is not known what clinical practice is being followed in the UK and the degree of variation.

Figures 1 and 2 show changes in referral times to secondary care and in times to use of DMARDs and steroids over 25 years in registered patients. Although there has been little change in referral times to secondary care (Fig. 1), there has been a favourable change in time to first DMARD therapy (Fig. 2). This figure also shows an increase in steroid use before secondary care involvement in the latter years. Figure 3 shows the changes in initial DMARD therapies since 1986. It was standard practice for SSZ (yellow bars) to be the first choice DMARD in the late 1980s in many rheumatology units, and the switch to MTX (red bars) has been more gradual than expected. Cessation of DMARD therapy was mainly due to loss or lack of effect rather than adverse events. The use of combination therapies at the outset was lower than expected, with triple therapy (SSZ, MTX and HCQ) featured in only very recent years. This graph does not include subsequent drug therapies, but step-up or add-on combination DMARD therapy was also not a common feature, 1–2% in the 1980s to 18% in 2008, and not in line with guidelines.

Fig. 1 Time in months from onset of symptoms to first rheumatology consultation. Horizontal bar: median; boxes: quartiles; whiskers: outliers.

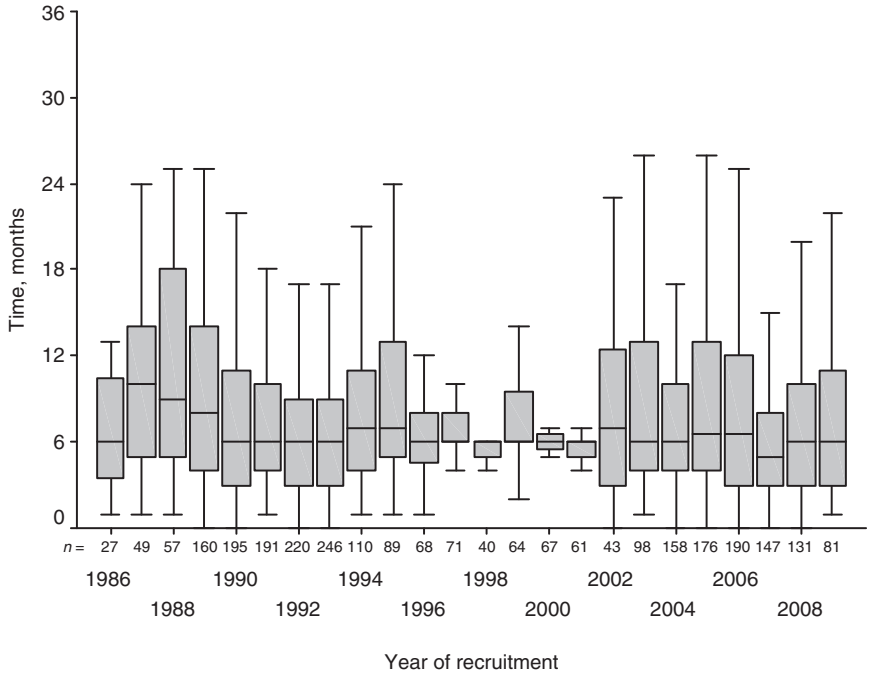
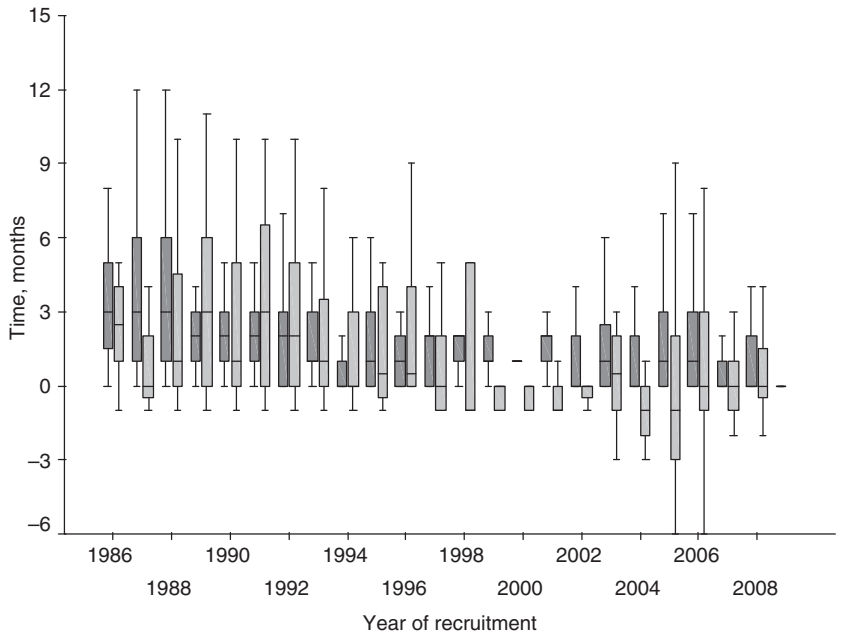
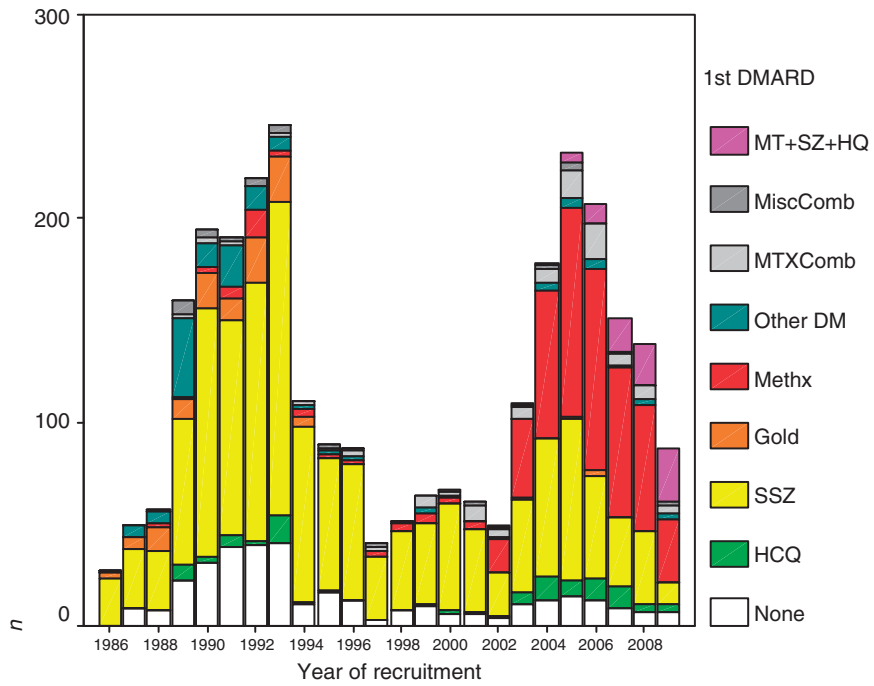


Fig. 2 Time in months from first rheumatology consultation to start of DMARD and steroid use. Dark bars: time in months from first outpatient attendance to first use of DMARDs; light bars: time in months from first outpatient attendance to first use of steroids.



There is evidence that these and similar graphs demonstrating comparative data between centres and sent as feedback reports to individual centres has prompted several types of responses to re-evaluate local practice. These include specialist trainee rheumatologists and nurse practitioners undertaking local audits, changes to departmental guidelines on early management, and departmental away days to discuss results.

FIG. 3 Initial DMARD use 1986–2009.



The current availability of national and local Hospital Episode Statistics (HES) data using ICD-10 and operating procedure codes [23] is another productive link between the early RA and national databases. Although data on hospital-based interventions became available in the late 1990s, diagnostic codes for these have only become reliable more recently, so that the network's targets for obtaining orthopaedic interventions for RA based on HES were not met initially, but data were collected by clinicians in outpatients. Poor patient recall and interventions performed in other hospitals would underestimate the surgery rates and make comparisons difficult. Despite this, the group reported surgery rates in patients recruited from 1986 to 1993 of 11% for large joint replacements or excision arthroplasties of hands or feet over the first 5 years of RA, at a median of 38 months from presentation [24]. The availability and quality of HES data have improved considerably, and a second report on 10 years of orthopaedic outcomes is in preparation.

A currently important topic in the management of RA is remission rates. The inception cohort design of this network has incorporated research issues; for example, the development of prognostic factors. One of the most powerful tools in the development of prognostic factors is whether predictive factors generated from one cohort can be confirmed in an independent but compatible cohort. The network has collaborated with the Early Arthritis Clinic (EAC) in Leiden to examine remission rates because of the similarity between the two cohorts. Although there was a difference in the frequency of sustained DMARD-free remission (9.4% in EAC compared with 15%) in the two cohorts, the two independent variables with predictive value identified in the EAC cohort, symptom duration at presentation and the absence of autoantibodies, were successfully validated in the second [26]. This is another example of one of the major strengths of this network, which is its ability to collaborate and share data with other organizations.

Conclusion

It has been recognized that the optimal treatment for early RA depends on the use of the best clinical practice and guidelines available, translating results of randomized studies into routine clinical practice, and defining and identifying patients with poor prognostic factors and poor responses to initial therapies. The problems with these items are that current 'good clinical practice' is known to vary, but little is known about actual practices carried out, and the highly selective, controlled nature and limited length of RCTs do not always relate to ordinary clinical settings. Prognostic factors are still not reliable enough to be used in routine clinical settings.

The RA database described here was designed to capture and reflect changes in clinical practice in ordinary clinical settings for the purpose of clinical governance issues and to measure different dimensions of outcome in patients treated with conventional therapy. The project has succeeded in providing this in 30 rheumatology centres, and further studies will be required to determine whether the provision of feedback data actually affects clinical practice, although valued by participating clinicians. In the present climate, few NHS Trusts are prepared to fund nurse practitioners to collect this

Table 2 Summary of strengths and weaknesses

Strengths	Weaknesses
Recruitment: 2866, mean ~120/year	Variable recruitment related mainly to funding issues. Only a small proportion of UK units involved. Some centres not always recruiting sequential patients
Fup: 0–25 years, mean 8 years	
Lost to Fup rates low	
Potential for UK wide participation	
All clinical assessments are standardized and comparable with other databases	Main source of missing data = drug start and stop dates ~10%
Different outcome dimensions reflect the real world including clinical remission [26], structural damage [9, 24], therapy [20, 28], mortality [16], comorbidity [17], functional [10] and work disability [27], health economics [29]	Currently limited criteria available for severity of comorbid conditions
Rapid reporting system for feedback loops with participating centres and some evidence of change in practice	Formal measurements of the affect of the register on clinical practice have as yet not been made, but indirect effects are apparent
Access to national databases, e.g. ONS and HES	Inaccurate or missing ICD-10 codes for primary and secondary diagnoses provided by HES
Collaborations and shared data projects, e.g. NAO, NICE, BSR and EAC	

Fup: follow-up.

information, which is limiting expansion of the network. Actual costs of the infrastructure for database management are relatively low. The strengths and weaknesses of this database are summarized in Table 2.

Rheumatology key messages

- RA registries can provide evidence on actual clinical practice in comparison with recommendations in guidelines.
- Results from RA registries are greatly enhanced by linkage with national databases.
- In order to achieve national involvement, RA registries require funding at the local level.

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